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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/954,950	09/18/2001	Pramod B. Mahajan	35718/238971 (5718-142)	8514

826 7590 04/20/2004

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EXAMINER	
KRUSE, DAVID H	
ART UNIT	**PAPER NUMBER**
1638	

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/954,950	MAHAJAN, PRAMOD B.	
	Examiner	Art Unit	
	David H Kruse	1638	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 29 March 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☒ ~~will not be~~ has been entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *1-3,6,10,11,13-16,19,20,23,27,28 and 32*.

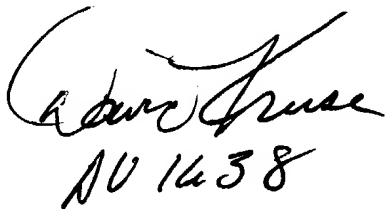
   Claim(s) withdrawn from consideration: _____.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☒ Other: See attached sequence search.

Continuation of 5. does NOT place the application in condition for allowance because: Applicant's arguments concerning the shared sequence similarity with the putative Arabidopsis MLH1 molecule has been addressed in the previous Office action (page 7, 1st paragrap of the Remarks). Applicant argues that Figure 2 sets forth a region of homology with the yeast MutL signature sequence in bold and that the art worker would find the combination of robust homology between a known MLH1/MutL molecule and Applicant's MLH1 molecule and the presence of a MutL signature sequence in Applicant's molecule to be strong evidence of the asserted utility (page 8, 1st paragraph o the Remarks). This argument is not found to be persuasive because the signature sequence to which Applicant refers does not define a protein with a specific function, but to a protein within the family of mismatch repair proteins of which MLH1/MutL is a member. The Examiner has attached a copy of the Office search report of Applicant's SEQ ID NO: 2, which shows that Applicant's asserted MLH1 has the same sequence identity, 67.5%, with both an Arabidopsis thaliana PMS2 protein (result 2) and a putative MLH1 protein (result 3). In addition, the sequence search report show that Applicant's asserted MLH1 protein is only 39.1% identical to the human MLH1 homologue (result 3) and has a higher similarity to the human PMS2 homologue at 39.3% (result 4) with almost identical local similarity. Applicants are directed to the Federal Register, Vol. 66, No. 4, January 5, 2001, page 1096, right column, 2nd paragraph, which states that where the class of proteins is defined by common structural features, but evidence shows that the members of the class do not share a specific, substantial functional attribute or utility, despite having structural features in common, membership in the class may not impute a specific, substantial and credible utility to a new member of the class. This response in essence addresses the remainder of Applicant's argument as to the rejections under 35 USC 101 and 112, first paragraph for enablement. As directed to the rejection under 35 USC 112, first paragraph, for written description at claim 32, Applicant argues that said claim recites nucleotide sequences having at least (about) 95% sequence identity to the sequence set forth in SEQ ID NO: 1 [in addition to encoding an MLH1 polypeptide having at least about 95% sequence identity to SEQ ID NO: 2] is a very predictable structure of the sequences encompassed by the claimed invention (page 14, 4th paragraph of the Remarks). This argument is not found to be persuasive because "predictability", while an issue of enablement, is not deemed to be high in the instant case because neither Applicant nor the art teaches how to predictable modify the amino acid structure o an MLH1 protein to produce variants.



```
DR   N-PSDB; AAD36728.
XX
PT   Novel rice MLH1 ortholog nucleic acid molecule for increasing
PT   efficiency of targeted gene mutation or homologous recombination in a
PT   plant and for generating plants with reversible male sterility -
XX
PS   Claim 7; Fig 2; 90pp; English.
XX
CC   The invention relates to isolated rice MLH1 orthologue nucleic acids. The
CC   nucleic acid is useful for increasing the efficiency of targetted gene
CC   mutation or homologous recombination in a plant, by transforming a plant
CC   with expression cassette comprising the nucleic acid linked to a chemical
CC   inducible promoter, transforming the plant with nucleic acid comprising
CC   a sequence having a desired mutation or a sequence to be homologously
CC   recombined, where the transformation occurs in the presence of chemical
CC   compound capable of inducing the promoter and the plant's cellular
CC   mismatch repair system is inhibited and selecting the transformed plants
CC   that contained the mutation or homologously recombined nucleotide
CC   sequence. The plant cellular mismatch repair system is inhibited through
CC   the use of transposon tagging of an MLH1 gene, sense- and antisense-
CC   suppression of an MLH1 gene, antibody binding to an MLH1 polypeptide or
CC   its variant, and targetted mutagenesis of specific amino acid residues
CC   encoded by an MLH1 gene. The nucleic acid is also useful for producing
CC   reversible male sterility in a plant, by transforming a plant with an
CC   expression cassette comprising a lexA DNA binding site embedded in a
CC   tissue-specific promoter that drives expression in the plant operably
CC   linked to the nucleic acid when expressed disrupts pollen formation or
CC   function through inhibition of the plant's cellular mismatch repair
CC   system, transforming the plant with a second expression cassette
CC   comprising a nucleotide sequence encoding a lexA repressor protein
CC   operably linked to a chemically-inducible promoter that drives expression
CC   in the plant, and exposing the plant to a compound capable of inducing
CC   the chemical-inducible promoter, to induce expression of lexA repressor
CC   protein. The tissue-specific promoter is an anther-specific promoter
CC   and the chemical-inducible promoter is a herbicidal safener. The
CC   polypeptide encoded by the nucleic acid is useful for detecting,
CC   locating, or removing a base pair mismatch (SNP). The present sequence
CC   is rice MLH1 protein.
XX
SQ   Sequence   724 AA;

  Query Match             100.0%;  Score 3709;  DB 23;  Length 724;
  Best Local Similarity   100.0%;  Pred. No. 1.8e-297;
  Matches  724;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy       1 MDEPSPRGGGCAGEPPRIRRLEESVVNRIAAGEVIQRPSSAVKELIENSLDAGASSVSVA 60
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1 MDEPSPRGGGCAGEPPRIRRLEESVVNRIAAGEVIQRPSSAVKELIENSLDAGASSVSVA 60

Qy      61 VKDGGLKLIQVSDDGHGIRFEDLAILCERHTTSKLSAYEDLQTIKSMGFRGEALASMTYV 120
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      61 VKDGGLKLIQVSDDGHGIRFEDLAILCERHTTSKLSAYEDLQTIKSMGFRGEALASMTYV 120

Qy     121 GHVTVTTITEGQLHGYRVSYRDGVMENEPKPCAAVKGTQVMVENLFYNMVARKKTLQNSN 180
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     121 GHVTVTTITEGQLHGYRVSYRDGVMENEPKPCAAVKGTQVMVENLFYNMVARKKTLQNSN 180

Qy     181 DDYPKIVDFISRFAVHHINVTFSCRKHGANRADVHSASTSSRLDAIRSVYGASVVRDLIE 240
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     181 DDYPKIVDFISRFAVHHINVTFSCRKHGANRADVHSASTSSRLDAIRSVYGASVVRDLIE 240

Qy     241 IKVSYEDAADSIFKMDGYISNANYVAKKITMILFINDRLVDCTALKRAIEFVYSATLPQA 300
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     241 IKVSYEDAADSIFKMDGYISNANYVAKKITMILFINDRLVDCTALKRAIEFVYSATLPQA 300

Qy     301 SKPFIYMSIHLPSEHVDVNIHPTKKEVSLLNQERIIETIRNAIEEKLMNSNTTRIFQTQA 360
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     301 SKPFIYMSIHLPSEHVDVNIHPTKKEVSLLNQERIIETIRNAIEEKLMNSNTTRIFQTQA 360

Qy     361 LNLSGIAQANPQKDKVSEASMGSGTKSQKIPVSQMVRTDPRNPSGRLHTYWHGQSSNLEK 420
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     361 LNLSGIAQANPQKDKVSEASMGSGTKSQKIPVSQMVRTDPRNPSGRLHTYWHGQSSNLEK 420

Qy     421 KFDLVSVRNVVRSRRNQKDAGDLSSRHELLVEIDSSFHPGLLDIVKNCTYVGLADEAFAL 480
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     421 KFDLVSVRNVVRSRRNQKDAGDLSSRHELLVEIDSSFHPGLLDIVKNCTYVGLADEAFAL 480

Qy     481 IQHNTRLYLVNVVNISKELMYQQALCRFGNFNAIQLSEPAPLQELLVMALKDDELMSDEK 540
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     481 IQHNTRLYLVNVVNISKELMYQQALCRFGNFNAIQLSEPAPLQELLVMALKDDELMSDEK 540

Qy     541 DDEKLEIAEVNTEILKENAEMINEYFSIHIDQDGKLTRLPVVLDQYTPDMDRLPEFVLAL 600
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     541 DDEKLEIAEVNTEILKENAEMINEYFSIHIDQDGKLTRLPVVLDQYTPDMDRLPEFVLAL 600

Qy     601 GNDVTWDDEKECFRTVASAVGNFYALHPPILPNPSGNGIHLYKKNRDSMADEHAENDLIS 660
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     601 GNDVTWDDEKECFRTVASAVGNFYALHPPILPNPSGNGIHLYKKNRDSMADEHAENDLIS 660

Qy     661 DENDVDQELLAEAEAAWAQREWTIQHVLFPSMRLFLKPPKSMATDGTFVQVASLEKLYKI 720
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     661 DENDVDQELLAEAEAAWAQREWTIQHVLFPSMRLFLKPPKSMATDGTFVQVASLEKLYKI 720

Qy     721 FERC 724
           ||||
Db     721 FERC 724


RESULT 2
AAE08710
ID   AAE08710 standard; Protein; 737 AA.
XX
AC   AAE08710;
XX
DT   15-NOV-2001  (first entry)
XX
DE   Arabidopsis thaliana PMS2 protein homologue MLH.
XX
KW   Hypermutable plant; dominant negative allele; mismatch repair gene;
KW   MMR; cell line generation; PMS2; AtMLH.
XX
OS   Arabidopsis thaliana.
XX
PN   WO200161012-A1.
XX
PD   23-AUG-2001.
XX
PF   28-DEC-2000; 2000WO-US35397.
XX
PR   18-FEB-2000; 2000US-0183333.
XX
PA   (NICO/) NICOLAIDES N C.
PA   (GRAS/) GRASSO L.
PA   (SASS/) SASS P M.
PA   (KINZ/) KINZLER K.
PA   (VOGE/) VOGELSTEIN B.
XX
PI   Nicolaides NC,  Grasso L,  Sass PM,  Kinzler K,  Vogelstein B;
XX
DR   WPI; 2001-529913/58.
XX
PT   Making hypermutable cell, useful for generating hypermutable plants,
PT   especially crop plants with new output traits, comprises introducing
PT   polynucleotide comprising dominant negative allele of mismatch repair
PT   gene into plant cell -
XX
PS   Example 1; Page 57-59; 72pp; English.
XX
CC   The invention relates to a method for generating hypermutable cell.
CC   The method involves introducing into a plant cell a polynucleotide
CC   comprising a dominant negative allele of a mismatch repair (MMR) gene.
CC   The method is useful for generating hypermutable plants, new cell lines
CC   and plant varieties. This is particularly useful for agriculturally
CC   important crops. The method is also useful for generating crop plants
CC   with new output traits and plant cells exhibiting new biochemicals for
CC   commercial use. The present sequence is Arabidopsis thaliana (At)
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CC   MLH protein. This sequence is a homologue of MMR protein, PMS2.
XX
SQ   Sequence   737 AA;

  Query Match             67.5%;  Score 2505;  DB 22;  Length 737;
  Best Local Similarity   66.4%;  Pred. No. 5.9e-198;
  Matches  482;  Conservative  111;  Mismatches  129;  Indels    4;  Gaps    3;

Qy       2 DEPSPRGGGCAGEPPRIRRLEESVVNRIAAGEVIQRPSSAVKELIENSLDAGASSVSVAV 61
           :| ||        |||:|:||||||||||||||||||| |||||:|||||| :||:|| |
Db      13 EEESPATTIVPREPPKIQRLEESVVNRIAAGEVIQRPVSAVKELVENSLDADSSSISVVV 72

Qy      62 KDGGLKLIQVSDDGHGIRFEDLAILCERHTTSKLSAYEDLQTIKSMGFRGEALASMTYVG 121
           |||||||||||||||||| ||| |||||||||||: :||| :: ||||||||||||||||
Db      73 KDGGLKLIQVSDDGHGIRREDLPILCERHTTSKLTKFEDLFSLSSMGFRGEALASMTYVA 132

Qy     122 HVTVTTITEGQLHGYRVSYRDGVMENEPKPCAAVKGTQVMVENLFYNMVARKKTLQNSND 181
           ||||||||:||:|||||||||||||:||| |||||||:|||||||||:||:|||||| |
Db     133 HVTVTTITKGQIHGYRVSYRDGVMEHEPKACAAVKGTQIMVENLFYNMIARRKTLQNSAD 192

Qy     182 DYPKIVDFISRFAVHHINVTFSCRKHGANRADVHSASTSSRLDAIRSVYGASVVRDLIEI 241
           || |||| :|| |:|: ||:|||||||| :|||||  : ||||:|||||| || ::|:::
Db     193 DYGKIVDLLSRMAIHYNNVSFSCRKHGAVKADVHSVVSPSRLDSIRSVYGVSVAKNLMKV 252

Qy     242 KVSYEDAADSIFKMDGYISNANYVAKKITMILFINDRLVDCTALKRAIEFVYSATLPQAS 301
           :||  |::   | |:|:|||:|||||  ::|||||||:|:|||||| ||:||||:||
Db     253 EVSSCDSSGCTFDMEGFISNSNYVAKKTILVLFINDRLVECSALKRAIEIVYAATLPKAS 312

Qy     302 KPFIYMSIHLPSEHVDVNIHPTKKEVSLLNQERIIETIRNAIEEKLMNSNTTRIFQTQAL 361
           |||:||||:|| ||||:|||||||||||||| ||| |:: :| || |:| || || | :
Db     313 KPFVYMSINLPREHVDINIHPTKKEVSLLNQEIIIEMIQSEVEVKLRNANDTRTFQEQKV 372

Qy     362 NLSGIAQANPQKDKVSEASMGSGTKSQKIPVSQMVRTDPRNPSGRLHTYWHGQSSNLEKK 421
               :   ||     :   || |:||:||::|||||  :|:|||| :   :  :| |
Db     373 EYIQ-STLTSQKSDSPVSQKPSGQKTQKVPVNKMVRTDSSDPAGRLHAFLQPKPQSLPDK 431

Qy     422 FDLVS-VRNVVRSRRNQKDAGDLSSRHELLVEIDSSFHPGLLDIVKNCTYVGLADEAFAL 480
             :| ||: || ||| |:  |||  ||:  :|| |||:|: |:|||||:||: |||
Db     432 VSSLSVVRSSVRQRRNPKETADLSSVQELIAGVDSCCHPGMLETVRNCTYVGMADDVFAL 491

Qy     481 IQHNTRLYLVNVVNISKELMYQQALCRFGNFNAIQLSEPAPLQELLVMALKDDEL--MSD 538
           :|:|| ||| ||||:|||||||| | || :|||||||:|||| ||:::|||:::|   :|
Db     492 VQYNTHLYLANVVNLSKELMYQQTLRRFAHFNAIQLSDPAPLSELILLALKEEDLDPGND 551

Qy     539 EKDDEKLEIAEVNTEILKENAEMINEYFSIHIDQDGKLTRLPVVLDQYTPDMDRLPEFVL 598
            ||| |  |||:|||:||| |||: |||:|||    |:||||:|||||||||:|||:|
Db     552 TKDDLKERIAEMNTELLKEKAEMLEEYFSVHIDSSANLSRLPVILDQYTPDMDRVPEFLL 611

Qy     599 ALGNDVTWDDEKECFRTVASAVGNFYALHPPILPNPSGNGIHLYKKNRDSMADEHAENDL 658
           ||||| |:||| ||: |::|:|||||:|||:|||||:||  | |  :|  ::
Db     612 CLGNDVEWEDEKSCFQGVSAAIGNFYAMHPPLLPNPSGDGIQFYSKRGESSQEKSDLEGN 671

Qy     659 ISDENDVDQELLAEAEAAWAQREWTIQHVLFPSMRLFLKPPKSMATDGTFVQVASLEKLY 718
           :  |:::|:||::|| |||||||:|||||||||||||||| |||::||||:||||||||
Db     672 VDMEDNLDQDLLSDAENAWAQREWSIQHVLFPSMRLFLKPPASMASNGTFVKVASLEKLY 731

Qy     719 KIFERC 724
           ||||||
Db     732 KIFERC 737


RESULT 3
AAE22979
ID   AAE22979 standard; Protein; 737 AA.
XX
AC   AAE22979;
XX
DT   21-AUG-2002  (first entry)
XX
DE   Arabidopsis thaliana MLH1 protein.
XX
KW   MLH1; gene mutation; mismatch repair system; transposon tagging;
KW   tissue-specific promoter; herbicidal safener; male sterility; detection;
KW   pollen formation; base pair mismatch.
XX
OS   Arabidopsis thaliana.
XX
PN   WO200224890-A2.
XX
PD   28-MAR-2002.
XX
PF   18-SEP-2001; 2001WO-US29088.
XX
PR   18-SEP-2000; 2000US-233124P.
XX
PA   (PION-) PIONEER HI-BRED INT INC.
XX
PI   Mahajan PB;
XX
DR   WPI; 2002-416283/44.
DR   N-PSDB; AAD36729.
XX
PT   Novel rice MLH1 ortholog nucleic acid molecule for increasing
PT   efficiency of targeted gene mutation or homologous recombination in a
PT   plant and for generating plants with reversible male sterility -
XX
PS   Disclosure; Page 89-90; 90pp; English.
XX
CC   The invention relates to isolated rice MLH1 orthologue nucleic acids. The
CC   nucleic acid is useful for increasing the efficiency of targetted gene
CC   mutation or homologous recombination in a plant, by transforming a plant
CC   with expression cassette comprising the nucleic acid linked to a chemical
CC   inducible promoter, transforming the plant with nucleic acid comprising
CC   a sequence having a desired mutation or a sequence to be homologously
CC   recombined, where the transformation occurs in the presence of chemical
CC   compound capable of inducing the promoter and the plant's cellular
CC   mismatch repair system is inhibited and selecting the transformed plants
CC   that contained the mutation or homologously recombined nucleotide
CC   sequence. The plant cellular mismatch repair system is inhibited through
CC   the use of transposon tagging of an MLH1 gene, sense- and antisense-
CC   suppression of an MLH1 gene, antibody binding to an MLH1 polypeptide or
CC   its variant, and targetted mutagenesis of specific amino acid residues
CC   encoded by an MLH1 gene. The nucleic acid is also useful for producing
CC   reversible male sterility in a plant, by transforming a plant with an
CC   expression cassette comprising a lexA DNA binding site embedded in a
CC   tissue-specific promoter that drives expression in the plant operably
CC   linked to the nucleic acid when expressed disrupts pollen formation or
CC   function through inhibition of the plant's cellular mismatch repair
CC   system, transforming the plant with a second expression cassette
CC   comprising a nucleotide sequence encoding a lexA repressor protein
CC   operably linked to a chemically-inducible promoter that drives expression
CC   in the plant, and exposing the plant to a compound capable of inducing
CC   the chemical-inducible promoter, to induce expression of lexA repressor
CC   protein. The tissue-specific promoter is an anther-specific promoter
CC   and the chemical-inducible promoter is a herbicidal safener. The
CC   polypeptide encoded by the nucleic acid is useful for detecting,
CC   locating, or removing a base pair mismatch (SNP). The present sequence
CC   is Arabidopsis thaliana MLH1 protein.
XX
SQ   Sequence   737 AA;

  Query Match             67.5%;  Score 2505;  DB 23;  Length 737;
  Best Local Similarity   66.4%;  Pred. No. 5.9e-198;
  Matches  482;  Conservative  111;  Mismatches  129;  Indels    4;  Gaps    3;

Qy       2 DEPSPRGGGCAGEPPRIRRLEESVVNRIAAGEVIQRPSSAVKELIENSLDAGASSVSVAV 61
           :| ||        |||:|:||||||||||||||||||| |||||:|||||| :||:|| |
Db      13 EEESPATTIVPREPPKIQRLEESVVNRIAAGEVIQRPVSAVKELVENSLDADSSSISVVV 72

Qy      62 KDGGLKLIQVSDDGHGIRFEDLAILCERHTTSKLSAYEDLQTIKSMGFRGEALASMTYVG 121
           |||||||||||||||||| ||| |||||||||||: :||| :: ||||||||||||||||
Db      73 KDGGLKLIQVSDDGHGIRREDLPILCERHTTSKLTKFEDLFSLSSMGFRGEALASMTYVA 132

Qy     122 HVTVTTITEGQLHGYRVSYRDGVMENEPKPCAAVKGTQVMVENLFYNMVARKKTLQNSND 181
           ||||||||:||:|||||||||||||:||| |||||||:|||||||||:||:|||||| |
Db     133 HVTVTTITKGQIHGYRVSYRDGVMEHEPKACAAVKGTQIMVENLFYNMIARRKTLQNSAD 192
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Qy     182 DYPKIVDPISRFAVHHINVTFSCRKHGANRADVHSASTSSRLDAIRSVYGASVVRDLIEI 241
           || |||| :|| |:|: ||:|||||||| :|||||  : ||||:|||||| || ::|::: 
Db     193 DYGKIVDLLSRMAIHYNNVSFSCRKHGAVKADVHSVVSPSRLDSIRSVYGVSVAKNLMKV 252

Qy     242 KVSYEDAADSIFKMDGYISNANYVAKKITMILFINDRLVDCTALKRAIEFVYSATLPQAS 301
           :||  |:: :  | |:|:|||:|||||  ::|||||||:|:|||||| ||:|||:|| 
Db     253 EVSSCDSSGCTFDMEGFISNSNYVAKKTILVLFINDRLVECSALKRAIEIVYAATLPKAS 312

Qy     302 KPFIYMSIHLPSEHVDVNIHPTKKEVSLLNQERIIETIRNAIEEKLMNSNTTRIFQTQAL 361
           {||:||||:|| ||||:|||||||||||||| ||| |:: :| || |:| || || | : 
Db     313 KPFVYMSINLPREHVDINIHPTKKEVSLLNQEIIIEMIQSEVEVKLRNANDTRTFQEQKV 372

Qy     362 NLSGIAQANPQKDKVSEASMGSGTKSQKIPVSQMVRTDPRNPSGRLHTYWHGQSSNLEKK 421
               :   ||      :   || |:||:||::|||||  :|:|||| :   :  :|  | 
Db     373 EYIQ-STLTSQKSDSPVSQKPSGQKTQKVPVNKMVRTDSSDPAGRLHAFLQPKPQSLPDK 431

Qy     422 FDLVS-VRNVVRSRRNQKDAGDLSSRHELLVEIDSSFHPGLLDIVKNCTYVGLADEAFAL 480
           :| ||: || ||| |:  |||| ||:  :|| |||:|: |:|||||:|:|: |||
Db     432 VSSLSVVRSSVRQRRNPKETADLSSVQELIAGVDSCCHPGMLETVRNCTYVGMADDVFAL 491

Qy     481 IQHNTRLYLVNVVNISKELMYQQALCRFGNFNAIQLSEPAPLQELLVMALKDDEL--MSD 538
           :|:|| ||| ||||:|||||||| | || :|||||||:|||| ||:::|||:::|   :| 
Db     492 VQYNTHLYLANVVNLSKELMYQQTLRRFAHFNAIQLSDPAPLSELILLALKEEDLDPGND 551

Qy     539 EKDDEKLEIAEVNTEILKENAEMINEYFSIHIDQDGKLTRLPVVLDQYTPDMDRLPEFVL 598
            ||| |  |||:|||:||| |||: ||||:||| |:||||:|||||||||||:|||:| 
Db     552 TKDDLKERIAEMNTELLKEKAEMLEEYFSVHIDSSANLSRLPVILDQYTPDMDRVPEFLL 611

Qy     599 ALGNDVTWDDEKECFRTVASAVGNFYALHPPILPNPSGNGIHLYKKNRDSMADEHAENDL 658
           ||||| |:||| ||: |::|:|||||:|||:|||||:|| .| |  :|  ::  
Db     612 CLGNDVEWEDEKSCFQGVSAAIGNFYAMHPPLLPNPSGDGIQFYSKRGESSQEKSDLEGN 671

Qy     659 ISDENDVDQELLAEAEAAWAQREWTIQHVLFPSMRLFLKPPKSMATDGTFVQVASLEKLY 718
           :  |:::||:||::|| |||||||:|||||||||||||||| |||::||||:|||||||| 
Db     672 VDMEDNLDQDLLSDAENAWAQREWSIQHVLFPSMRLFLKPPASMASNGTFVKVASLEKLY 731

Qy     719 KIFERC 724
           ||||||
Db     732 KIFERC 737
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RESULT 4
AAW09036
ID AAW09036 standard; protein; 752 AA.
XX
AC AAW09036;
XX
DT 01-OCT-1997 (first entry)
XX
DE Mismatch repair protein, hPMS2.
XX
KW Human; mismatch repair protein; hMSH2; hMLH1; hPMS2; antibody; Ab;
KW proliferation; anti-cancer therapy; neoplastic tissue; DNA replication;
KW DNA repair; mutation; sporadic colorectal carcinoma; cancer; HNPCC;
KW inherited; non-polyposis colorectal carcinoma.
XX
OS Homo sapiens.
XX
PN WO9641192-A1.
XX
PD 19-DEC-1996.
XX
PF 07-JUN-1996; 96WO-US08957.
XX
PR 07-JUN-1995; 95US-0480351.
XX
PA (UYJO) UNIV JOHNS HOPKINS.
XX
PI Burrell M, Hill DE, Kinzler KW, Vogelstein B;
XX
DR WPI; 1997-077287/07.
XX
PT Discriminating proliferating from non-proliferating cells in tissue
PT - using antibodies specifically immuno-reactive with mismatch repair
PT protein, esp. human MSH2
XX
PS Disclosure; Page 23-25; 37pp; English.
XX
CC The sequences given in AAW09034-36 represent the human mismatch repair
CC proteins, hMSH2, hMLH1 and hPMS2. In the method of the invention, these
CC proteins were identified by reaction with an antibody (Ab) specific for
CC them, therefor discriminating proliferating from non-proliferating cells
CC The method may be used for monitoring the effectiveness of anti-cancer
CC therapy in neoplastic tissue, by comparing the amount of Ab-Ag complexes
CC in the sample with an amount determined at an earlier time, in which a
CC reduction in the amount indicates an effective therapy. The Ab are
CC especially specifically immunoreactive with the MSH2 mismatch repair
CC gene, which is 1 of at least 4 genes encoding proteins involved in the
CC repair of mismatched nucleotides following DNA replication or repair.
CC Mutations in the MSH2 gene contribute to the development of sporadic
CC colorectal carcinoma, while germline MSH2 mutations are responsible for
CC approx. 50% of inherited, non-polyposis colorectal carcinoma (HNPCC).
CC Since MSH2 is ubiquitously expressed, development of other cancers are
CC also susceptible to alterations in MSH2.
XX
SQ Sequence 752 AA;

Query Match 39.3%; Score 1457; DB 18; Length 752;
Best Local Similarity 39.7%; Pred. No. 2.5e-111;
Matches 311; Conservative 146; Mismatches 212; Indels 114; Gaps 11;

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Qy      18 IRRLEESVVNRIAAGEVIQRPSSAVKELIENSLDAGASSVSVAVKDGGLKLIQVSDDGHG 77
           ||||:|:|||||||||||||::|:||:||| ||| ::|: | ||:|||||||: |:| |
Db       8 IRRLDETVVNRIAAGEVIQRPANAIKEMIENCLDAKSTSIQVIVKEGGLKLIQIQDNGTG 67

Qy      78 IRFEDLAILCERHTTSKLSAYEDLQTIKSMGFRGEALASMTYVGHVTVTTITEGQLHGYR 137
           || ||| |:||| ||||| ::||| :| : |||||||||:::| |||:|| |    ||
Db      68 IRKEDLDIVCERFTTSKLQSFEDLASISTYGFRGEALASISHVAHVTITTKTADGKCAYR 127

Qy     138 VSYRDGVMENEPKPCAAVKGTQVMVENLFYNMVARKKTLQNSNDDYPKIVDFISRFAVHH 197
           || || ::  |||||  :|||: ||:|||:  |:| |:| :::| ||:: : |::||:
Db     128 ASYSDGKLKAPPKPCAGNQGTQITVEDLFYNIATRRKALKNPSEEYGKILEVVGRYSVHN 187

Qy     198 INVTFSCRKHGANRADVHSASTSSRLDAIRSVYGASVVRDLIEIKVSYEDAADSIFKMDG 257
             ::|| :| |   ||| :   :| :| |||::| :| |:|||     :  |   |||:|
Db     188 AGISFSVKKQGETVADVRTLPNASTVDNIRSIFGNAVSRELIEIGCEDKTLA---FKMNG 244

Qy     258 YISNANYVAKKITMILFINDRLVDCTALKRAIEFVYSATLPQASKPFIYMSIHLPSEHVD 317
           |||||||  ||   :|||| |||: |:|::||| ||:| ||: : ||:|:|: :  ::||
Db     245 YISNANYSVKKCIFLLFINHRLVESTSLRKAIETVYAAYLPKNTHPFLYLSLEISPQNVD 304

Qy     318 VNIHPTKKEVSLLNQERIIETIRNAIEEKLMNSNTTRIFQTQALNLSGIAQANPQ--KDK 375
           ||:|||| ||  |::| |:| ::  || ||: ||::|:: || | | |:|  : :  |
Db     305 VNVHPTKHEVHFLHEESILERVQQHIESKLLGSNSSRMYFTQTL-LPGLAGPSGEMVKST 363

Qy     376 VSEASMGSGTKSQKIPVSQMVRTDPRNPSGRLHTYWHGQSSNL---------EKKFDLVS 426
           | |  :   | |:   ||||||  |    :|  :   |  |           | | |: |
Db     364 TSLTSSSTSGSSDKVYAHQMVRTDSREQ--KLDAFLQPLSKPLSSQPQAIVTEDKTDISS 421

Qy     427 VRNVVR------------SRRNQKDAGDLS---------------------------- 444
           |  :                : :||  || :
Db     422 GRARQQDEEMLELPAPAEVAAKNQSLEGDTTKGTSEMSEKRGPTSSNPRKRHREDSDVEM 481

Qy     445 ----SRHELLV-------------------EIDSSFHPGLLDIVKNCTYVGLADEAFALI 481
               || |:                     ||:   |  | ::: | ::||  :  :||
Db     482 VEDDSRKEMTAACTPRRRIINLTSVLSLQEEINEQGHEVLREMLHNHSFVGCVNPQWALA 541

Qy     482 QHNTRLYLVNVVNISKELMYQQALCRFGNFNAIQLSEPAPLQELLVMALKDDELMSDEKD 541
           || |:|||:|   :|:|| ||  :  | ||  ::|||||| :| ::||  |    |:|
Db     542 QHQTKLYLLNTTKLSEELFYQILIYDFANFGVLRLSEPAPLFDLAMLALDSPESGWTEED 601

Qy     542 DEKLEIAEVNTEILKENAEMINEYFSIHIDQDGKLTRLPVVLDQYTPDMDRLPEFVLALG 601
           |  :||  | ||: |||: :|||: ||::| |  ||:::| | | :: || |:| |
Db     602 GPKEGLAEYIVEFLKKKAEMLADYFSLEIDEEGNLIGLPLLIDNYVPPLEGLPIFILRLA 661
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```
Qy    602 NDVTWDDEKECFRTVASAVGNFYALHPPILPNPSGNGIHLYKKNRDSMADEHAENDLISD 661
          :| ||:||||| :::     ||::                                  ||:
Db    662 TEVNWDEEKECFESLSKECAMFYSI----------------------------RKQYISE 693

Qy    662 ENDVDQELLAEAEAAWAQREWTIQHVLFPSMRLFLKPPKSMATDGTFVQVASLEKLYKIF 721
          |: :  :  :|   :|   :||::|::: ::|  : |||    ||  :|:|:|  |||:|
Db    694 ESTLSGQ-QSEVPGSW---KWTVEHIVYKALRSHILPPKHFTEDGNILQLANLPDLYKVF 749

Qy    722 ERC 724
          |||
Db    750 ERC 752


RESULT 5
AAR75785
ID   AAR75785 standard; Protein; 756 AA.
XX
AC   AAR75785;
XX
DT   04-MAR-1996  (first entry)
XX
DE   Human wild type MLH1, a MutL homologue.
XX
KW   hMLH1; wild type; MutL homologue; cancer diagnosis; mismatch repair;
KW   tumour; susceptibility; mutation detection.
XX
OS   Homo sapiens.
XX
PN   WO9516793-A1.
XX
PD   22-JUN-1995.
XX
PF   16-DEC-1994;   94WO-US14746.
XX
PR   09-DEC-1994;   94US-0352902.
PR   17-DEC-1993;   93US-0168877.
PR   08-MAR-1994;   94US-0209521.
XX
PA   (DAND ) DANA FARBER CANCER INST INC.
PA   (UYOR-) UNIV OREGON HEALTH SCI.
XX
PI   Baker SM,  Bollag RJ,  Bronner CE,  Kolodner RD,  Liskay RM;
XX
DR   WPI; 1995-231583/30.
DR   N-PSDB; AAQ90814.
XX
PT   Determn. of a mutation in a mutL homologue or gene prod. in a tissue
PT   - used to diagnose cancer susceptibility, and to identify and
PT   classify a DNA mismatch-repair-defective tumour
XX
PS   Claim 33; Fig 3; 168pp; English.
XX
CC   AAQ90814 encodes AAR75785 the wild type hMLH1, a MutL homologue. A
CC   mutation in a hMLH1 or hPMS1 nucleic acid isolated from a subject,
CC   can be detected by comparing it with an analogous segment of the
CC   above wild type allele. This method can be used to diagnose cancer
CC   susceptibility, or to identify and classify a DNA mismatch-repair
CC   defective tumour.
XX
SQ   Sequence   756 AA;

  Query Match           39.1%;  Score 1452;  DB 16;  Length 756;
  Best Local Similarity   39.6%;  Pred. No. 6.5e-111;
  Matches  311;  Conservative  145;  Mismatches  214;  Indels  116;  Gaps   11;

Qy     18 IRRLEESVVNRIAAGEVIQRPSSAVKELIENSLDAGASSVSVAVKDGGLKLIQVSDDGHG 77
          ||||:|:|||||||||||||::|:||:||| ||| ::|: | ||:|||||||: |:| |
Db      8 IRRLDETVVNRIAAGEVIQRPANAIKEMIENCLDAKSTSIQVIVKEGGLKLIQIQDNGTG 67

Qy     78 IRFEDLAILCERHTTSKLSAYEDLQTIKSMGFRGEALASMTYVGHVTVTTITEGQLHGYR 137
          || ||| |:||| ||||| ::||| :| : ||||||||||:::| |||:|| |      ||
Db     68 IRKEDLDIVCERFTTSKLQSFEDLASISTYGFRGEALASISHVAHVTITTKTADGKCAYR 127

Qy    138 VSYRDGVMENEPKPCAAVKGTQVMVENLFYNMVARKKTLQNSNDDYPKIVDFISRFAVHH 197
          || || ::  |||||  :|||: ||:|||||:  |:| |:| :::| ||:: : |::||:
Db    128 ASYSDGKLKAPPKPCAGNQGTQITVEDLFYNIATRRKALKNPSEEYGKILEVVGRYSVHN 187

Qy    198 INVTFSCRKHGANRADVHSASTSSRLDAIRSVYGASVVRDLIEIKVSYEDAADSIFKMDG 257
            ::|| :| |   ||| :   :| :| |||::| :| |:|||| :  |  |||:|
Db    188 AGISFSVKKQGETVADVRTLPNASTVDNIRSIFGNAVSRELIEIGCEDKTLA---FKMNG 244

Qy    258 YISNANYVAKKITMILFINDRLVDCTALKRAIEFVYSATLPQASKPFIYMSIHLPSEHVD 317
          |||||||  ||  :|||| ||| |:|:::||| ||:| ||: : ||:|:|: :  ::||
Db    245 YISNANYSVKKCIFLLFINHRLVESTSLRKAIETVYAAYLPKNTHPFLYLSLEISPQNVD 304

Qy    318 VNIHPTKKEVSLLNQERIIETIRNAIEEKLMNSNTTRIFQTQALNLSGIAQANPQ--KDK 375
          ||:|||| ||  |::| |:| ::  || ||: ||::|:: || | | |:|  : :  |
Db    305 VNVHPTKHEVHFLHEESILERVQQHIESKLLGSNSSRMYFTQTL-LPGLAGPSGEMVKST 363

Qy    376 VSEASMGSGTKSQKIPVSQMVRTDPRNPSGRLHTYWHGQSSNL---------EKKFDLVS 426
          |  |  :  | |:   ||||| |    :|  :    |  |          | | |: |
Db    364 TSLTSSSTSGSSDKVYAHQMVRTDSREQ--KLDAFLQPLSKPLSSQPQAIVTEDKTDISS 421

Qy    427 VRNVVR-------------SRRNQKDAGDLS---------------------------- 444
          |   :               : :||   || :
Db    422 GRARQQDEEMLELPAPAEVAAKNQSLEGDTTKGTSEMSEKRGPTSSNPRKRHREDSDVEM 481

Qy    445 ----SRHELLV------------------EIDSSFHPGLLDIVKNCTYVGLADEAFALI 481
              || |:                    ||:   |  | ::: | ::||  :  :||
Db    482 VEDDSRKEMTAACTPRRRIINLTSVLSLQEEINEQGHEVLREMLHNHSFVGCVNPQWALA 541

Qy    482 QHNTRLYLVNVVNISKELMYQQALCRFGNFNAIQLSEPAPLQELLVMALKDDELMSDEKD 541
          || |:|||:|   :|:|| ||  :  | ||  ::|||||| :| ::||   |    |:|
Db    542 QHQTKLYLLNTTKLSEELFYQILIYDFANFGVLRLSEPAPLFDLAMLALDSPESGWTEED 601

Qy    542 DEKLEIAEVNTEILKENAEMINEYFSIHIDQDGKLTRLPVVLDQYTPDMDRLPEFVLALG 601
          |  :||   | ||: |||: :|||: ||::| |  ||:::| | | :: || |:| |
Db    602 GPKEGLAEYIVEFLKKKAEMLADYFSLEIDEEGNLIGLPLLIDNYVPPLEGLPIFILRLA 661

Qy    602 NDVTWDDEKECFRTVASAVGNFYALHPPILPNPSGNGIHLYKKNRDSMADEHAENDLISD 661
          :| ||:||||| :::     ||::                                  ||:
Db    662 TEVNWDEEKECFESLSKECAMFYSI----------------------------RKQYISE 693

Qy    662 ENDV---DQELLAEAEAAWAQREWTIQHVLFPSMRLFLKPPKSMATDGTFVQVASLEKLY 718
          |: :    |:    :|   :||::|::: ::|  : |||    ||  :|:|:|  ||
Db    694 ESTLSGQQSEVPGSIPNSW---KWTVEHIVYKALRSHILPPKHFTEDGNILQLANLPDLY 750

Qy    719 KIFERC 724
          |:|||
Db    751 KVFERC 756


RESULT 6
AAR76071
ID   AAR76071 standard; Protein; 756 AA.
XX
AC   AAR76071;
XX
DT   15-JAN-1996  (first entry)
XX
DE   Human mismatch repair pathway protein, Mlh1.
XX
KW   Mismatch repair; MSH2; primer; identification; defect; alteration;
KW   cancer; tumour; vaccine.
XX
OS   Homo sapiens.
XX
PN   WO9514085-A2.
XX
PD   26-MAY-1995.
XX
PF   17-NOV-1994;   94WO-US13385.
XX
PR   13-JUN-1994;   94US-0259310.
PR   17-NOV-1993;   93US-0154792.
PR   07-DEC-1993;   93US-0163449.
```